Docket No.: PF-0148-3 CPA

EXPEDITED PROCEDURE
EXAMINING GROUP 1652

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of: Hawkins et al.

Title:	A NOVEL HUMAN PYROPHOSPHATASE		
Serial No.:	09/415,540	Filing Date:	October 8, 1999
Examiner:	Slobodyansky, E.	Group Art Unit:	1652

BOX AF
Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed September 19, 2001, and received at the Patent Office on September 24, 2001, the 24th being a Saturday, herewith are three copies of Appellants' Brief on Appeal. Authorized fees include the statutory fee of $320.00 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 18, 19, and 20-22 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Genomics, Inc.), (Reel 8437, Frame 0115) who is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 18-22
Claims allowed:	none
Claims canceled:	none
Claims withdrawn:	Claim 1
Claims on Appeal:	Claims 18-22

(4) STATUS OF AMENDMENTS AFTER FINAL

No amendments were submitted following receipt of the Final Rejection.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to isolated polynucleotides encoding polypeptides identified as a novel human pyrophosphatase (HPYP), and to a method of detecting those polynucleotides in a sample.

Nucleic acids encoding HPYP were first identified in Incyte Clone 768320 from the lung tissue cDNA library LUNGNOTO4 through a computer-generated search for amino acid sequence alignments. HPYP is 289 amino acids in length and shares both chemical and structural homology with the partial sequence of a human pyrophosphatase (GI 727225; SEQ ID NO:3), a bovine pyrophosphatase (GI 585322, SEQ ID NO:4) and a yeast pyrophosphatase (GI 4199; SEQ ID NO:5). In particular, HPYP shares 77% identity with the partial human pyrophosphatase sequence (SEQ ID NO:3) over the length of that molecule. The bovine and yeast pyrophosphatases each share 96% and 37% identity with HPYP, respectively. Despite the wide variation in overall sequence identity

between these four molecules, all of them contain the seventeen amino acid residues previously identified as being important for pyrophosphatase activity (Lahti, R et al. (1990) Biochim Biophys Aca 1038:338-345). In particular, the sequence, DEGETDWK, beginning at amino acid residue D(148), is identical for all four molecules. As illustrated by Figures 3 and 4 of the Specification, HPYP and bovine pyrophosphatase have rather similar hydrophobicity plots. Northern analysis (Figure 5 of the Specification) shows the expression of this sequence in various libraries, at least 43% of which are immortalized or cancerous and at least 24% of which involve immune response. Of particular note is the expression in thyroid tissue, colon tumor and rheumatoid arthritis. Specification at page 10, line 24 to page 10, line16.

The polynucleotides of the present invention are useful, for example, in providing new diagnostic or therapeutic compositions useful in the treatment of diseases and conditions associated with uncontrolled cell signaling and cell proliferation such as inflammatory diseases and cancer.

(6) THE REJECTIONS

Claim 19, and dependent claims 18 and 20-22, stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description. In particular, the Examiner asserts

> With regard to a naturally-occurring human polynucleotide sequence variant, there is no description of any mutational site that exit [sic] in nature, and there is no description of how the structure of SEQ ID NO:2 relates to the structure of any allele including strictly neutral alleles. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes of the genus are not described. One of skill in the art would not conclude that the applicant was in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claims. Therefore, a naturally-occurring DNA encoding a polypeptide comprising a sequence having 90% identity to SEQ ID NO:1 lack sufficient written description needed to prctice the invention of claims 18-22. (Final Office Action of June 19, 2001, Paper No.22, pages 2-3).

(7) ISSUE

Whether the Specification as filed provides sufficient disclosure to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph as to a naturally-occurring human polynucleotide sequence variant encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1.

(8) GROUPING OF THE CLAIMS

As to the single issue on appeal, all of the claims on appeal are grouped together.

(9) APPELLANTS' ARGUMENTS

The rejection of Claims 18-22 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description is improper as the claimed subject matter is adequately described in the Specification.

Claim 19, with dependent claims 18 and 20-22, stand rejected under the first paragraph of 35 U.S.C. 112 for alleged lack of an adequate written description. This rejection is respectfully traversed.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of

> such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

In the present case, claim 19 in relevant part recites

> "An isolated polylnucleotide selected from the group consisting of ... b) a naturally-occurring human polynucleotide sequence variant encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1..."

Appellants respectfully assert that the the disclosure in the Specification as filed is more than sufficient to satisfy the written description requirement of as to the claimed subject matter. In particular, SEQ ID NO:1 and SEQ ID NO:2 are specifically disclosed in the application (see, for example, Figure 1A-D). Given the genetic code and SEQ ID NO:1, all possible polynucleotide sequences encoding SEQ ID NO:1 are therefore described. Variants of SEQ ID NO:2 which encode SEQ ID NO:1 are also explicitly described, for example, at page 11, line 26 through page 12, line 13.

Variants of the amino acid sequence of SEQ ID NO:1 are also described. In particular, the preferred, more preferred, and most preferred SEQ ID NO:1 variants (i.e., those having 80%, 90%, and 95% amino acid sequence similarity to SEQ ID NO:1) are described, for example, at page 11, lines 17-20. Finally, polynucleotide sequence variants which encode 90% homologs of SEQ ID NO:1 are described, for example, at page 12, lines 20-24, and at page 13, lines 7-14. The specification also describes (e.g., page 45, line 26 through page 46, line 18) how to use BLAST to determine whether a given sequence falls within the "at least 90% polypeptide sequence identity" scope.

Incyte clones in which the nucleic acids encoding the human HPYP protein were first identified and libraries from which those clones were isolated are described, for example, at page 10, lines 24-29 of the Specification. Chemical and structural features of HPYP are described, for example, on page 16, lines 10-18.

Therefore, given SEQ ID NO:1 and SEQ ID NO:2, one of ordinary skill in the art would recognize that Appellants were in possession of the claimed invention, i.e., naturally-occurring polynucleotide variants encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, as of the time of filing. Accordingly, the Specification provides an adequate written description of the recited polynucleotide sequences.

A. **The present claims specifically define the claimed genus through the recitation of chemical structure**

With respect to the sufficiency of the disclosure, the Examiner asserts

> "As noted by Applicants [Appellants herein] in reciting "Guidelines" [referring to the "Guidelines for Examination of Patent applications Under the 35 U.S.C. Sec 112, para.1", published January 5, 2001], "functional characteristics when coupled with a known or disclosed correlation between function and structure" may be sufficient to meet the written description requirement. In the instant case said correlation is not disclosed and a DNA encoding functionally unrelated proteins are encompassed. Function of said DNAs [sic] is unpredictable. While combination [sic] of structural and functional characteristics such as 90% identity and possession of pyrophosphatase activity may sufficiently describe the genus of the encompassed molecules, the structural characteristics alone such as 90% identity without function do not." Final Office Action pages 2-3.

Thus the Examiner in essence asserts that recitation of chemical structure alone is not sufficient to satisfy the written description requirement as to the claimed polynucleotide sequence variants. Such a position is believed to present a misapplication of the law as it has been interpreted by the Federal Circuit Court of Appeals.

Court cases in which "DNA claims" have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires

that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

In the *Fiers* case, the Revel party argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human

fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of claim 19 recites chemical structure to define the claimed genus:

> 19. An isolated polynucleotide selected from the group consisting of ... b) a naturally-occurring human polynucleotide sequence variant encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO: 1. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

B. The present claims do not define a genus which is highly variant

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <40%

overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding novel human inorganic pyrophosphatases related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as human pyrophosphatase proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, "a naturally-occurring human polynucleotide sequence variant encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 (note that SEQ ID NO:1 has 289 amino acid residues). This variation is far less than that of all potential human pyrophosphatase proteins related to SEQ ID NO:1, i.e., those human pyrophosphatase proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

The case of *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) provides further support for concluding that the polynucleotide genus defined by the present claims complies with the written description requirement. As discussed above, certain claims of U.S. Patent No. 4,652,525 were found invalid for failing to satisfy the written description requirement. The *Lilly* case, however, also considered U.S. Patent No. 4,431,740. While there is a discussion in *Lilly* of issues of infringement and enforceability of the claims of the '740 patent, there is no written description analysis of the claims of the '740 patent. However, there was no holding of invalidity of any claim of the '740 patent. Thus, the claims of the '740 patent are presumed to satisfy the written description of 35 U.S.C. §112. See 35 U.S.C. §282. Now consider, for example, claim 4 of the '740 patent, which reads as follows:

> 4. A DNA transfer vector comprising a deoxynucleotide sequence coding for human pre-proinsulin consisting essentially of a plus strand having the sequence:
>
> $5'\text{-}_{-24}$ GCL$_{-23}$ X$_{-22}$ TY$_{-22}$ TGG$_{-21}$ ATG$_{-20}$ W$_{-19}$ GZ$_{-19}$ X$_{-18}$ TY$_{-18}$ X$_{-17}$ TY$_{-17}$ CCL$_{-16}$ X$_{15}$TY$_{-15}$ X$_{-14}$ TY$_{-14}$ GCL$_{-13}$ X$_{-12}$ TY$_{-12}$ X$_{-11}$ TY$_{-11}$ GCL$_{-10}$ X$_{-9}$ TY$_{-9}$ TGG$_{-8}$ GGL$_{-7}$ CCL$_{6}$GAK$_{-5}$ CCL$_{-4}$ GCL$_{-3}$ GCL$_{-2}$ GCL$_{-1}$ TTK$_1$ GTL$_2$ AAK$_3$ CAJ$_4$ CAK$_5$ X$_6$ TY$_6$ TGK$_7$ GGL$_8$ QR$_9$ S$_9$ CAK$_{10}$ X$_{11}$ TY$_{11}$ GTL$_{12}$ GAJ$_{13}$ GCL$_{14}$ X$_{15}$ TY$_{15}$ TAK$_{16}$ X$_{17}$ TY$_{17}$

GTL_{18} TGK_{19} GCL_{20} GAJ_{21} W_{22} GZ_{22} GCL_{23} TTK_{24} TTK_{25} TAK_{26} ACL_{27} CCL_{28} AAJ_{29} ACL_{30} W_{31} GZ_{31} W_{32} GZ_{32} GAJ_{33} GCL_{34} GAJ_{35} GAK_{36} X_{37} TY_{37} CAJ_{38} GTL_{39} GGL_{40} CAJ_{41} GTL_{42} GAJ_{43} X_{44} TY_{44} GGL_{45} GGL_{46} GGL_{47} CCL_{48} GGL_{49} GCL_{50} GGL_{51} QR_{52} S_{52} X_{53} TY_{53} CAJ_{54} CCL_{55} X_{56} TY_{56} GCL_{57} X_{58} TY_{58} GAJ_{59} GGL_{60} QR_{61} S_{61} X_{62} TY_{62} CAJ_{63} AAJ_{64} W_{65} GZ_{65} GGL_{66} ATM_{67} GTL_{68} GAJ_{69} CAJ_{70} TGK_{71} TGK_{72} ACL_{73} QR_{74} S_{74} ATM_{75} TGK_{76} QR_{77} S_{77} X_{78} TY_{78} TAK_{79} CAJ_{80} X_{81} TY_{81} GAJ_{82} AAK_{83} TAK_{84} TGK_{85} AAK_{86} TAGACGCAGCCCGCAGGCAGCCCCCCACCCGCCGCCTCCTGCACCGAG AGAGATGGAATAAAGCCCTTGAACCA GC polyA-3'

wherein

A is deoxyadenyl,

G is deoxyguanyl,

C is deoxycytosyl,

T is thymidyl,

J is A or G;

K is T or C;

L is A, T, C, or G;

M is A, C or T;

X_n is T or C if Y_n is A or G; and C if Y_n is C or T;

Y_n is A, G, C or T if X_n is C, and A or G if X_n is T;

W_n is C or A if Z_n is G or A, and C if Z_n is C or T;

Z_n is A, G, C or T if W_n is C, and A or G if W_n is A;

QR_n is TC if S_n is A, G, C or T, and AG if S_n is T or C;

S_n is A, G, C or T if QR_n is TC, and T or C if QR_n is AG; and, script numerals, n, refer to the position in the amino acid sequence of human proinsulin, to which

each triplet in the nucleotide sequence corresponds, according to the genetic code, the amino acid positions being numbered from the amino end.

Claim 4 of the '740 patent recites a DNA sequence which includes the coding region for human pre-proinsulin; in particular, the 330 nucleotide bases from codon $-GCL_{24}$ through codon AAK_{86} code for human pre-proinsulin. As can be seen from the claim language, claim 4 of the '740 patent sets forth a DNA structure with numerous variant positions. Of the 330 nucleotides in the coding region for human pre-proinsulin, 141 are potentially variant positions within the structure defined by claim 4. Thus, claim 4 of the '740 patent defines a DNA which potentially is only 57% identical (189/330 x 100% = 57%) to the single species of human pre-proinsulin actually sequenced in the '740 patent. See Example 1 and Figure 2. As discussed above, the present claims encompass naturally-occurring polynucleotides encoding amino acid sequences having at least 90% sequence identity to the sequence of SEQ ID NO:1. Clearly, then, the genus variation of the present claims is less than that of claim 4 of the '740 patent.

C. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of October 31, 1996. Much has happened in the development of recombinant DNA technology in the 18 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been

compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

D. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

(10) CONCLUSION

The written description rejection with respect to the claimed "variants" should be reversed, based on at least the arguments presented above.

Respectfully submitted,

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Date: November 26th, 2001

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APPENDIX

Claims on appeal:

18. (Reiterated) The method of claim 20, wherein before hybridization, the target polynucleotide is amplified by the polymerase chain reaction.

19. (Reiterated) An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide sequence of SEQ ID NO:2,

b) a naturally-occurring human polynucleotide sequence variant encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, and

c) a polynucleotide sequence complementary to a) or b).

20. (Reiterated) A method of detecting a target polynucleotide in a sample, said target polyucleotide having the sequence of a polynucleotide of claim 19, comprising

hybridizing the sample with a probe comprising at least 15 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hyubridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and

detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

21. (Reiterated) A method of claim 20, wherein the probe comprises at least 30 contiguous nucleotides.

22. (Reiterated) A method of claim 20, wherein the probe comprises at least 60 contiguous nucleotides.